REMARKS

Claims 58-72 and 75-86 are rejected, under 35 U.S.C. § 103(a), as being unpatentable over Barton et al. `586 in view of Lee et al. `653. The Applicant acknowledges and respectfully traverses the raised obviousness rejection in view of the following remarks.

Firstly, in regards to the arguments raised by the Applicant in the response of July 10, 2003, and the Examiner's rebuttal that ".....one cannot show nonobviousness by attacking references individually....". The Applicant points out that the previously presented arguments, as well as those presented below, are expressly relative to the Examiner's combination of the individual Barton et al. `586, and Lee et al. `653 references, as well as to obviousness. In other words, the Applicant initially takes issue with the combination of the individual references that are being used by the Examiner to support a show of obviousness, and thus an analysis of what is disclosed, taught and suggested by each reference is believed proper.

There is an important distinction between arguing against the combination of the references, and that of arguing obviousness. The point of addressing each of the references individually is to show that the cited references are not only uncombinable, but that each reference, either alone or in combination with the other, does not render the presently claimed invention non-obvious.

As the Examiner is aware, in order to properly support an obviousness rejection under 35 U.S.C. § 103(a), the applied references by themselves must provide some disclosure, teaching or suggestion which would lead one of skill in the art to combine the references as suggested by the Examiner to achieve all the features of the presently claimed invention.

The Applicant points out that claim 58 has been amended to more clearly reflect the nature of the presently claimed invention with respect to the applied Barton et al. `586 reference by specifically reciting, "A nucleic acid oligomer modified by attaching a non-intercalative catalytically redox-active moiety.....". As previously discussed, Barton et al. `586 is concerned with methods for the detection of genetic point mutations in nucleic acid sequences and its application to a biosensor (column 5, line 66 to column 6, line 1). According to

Barton et al. `586, an intercalative, redox-active moiety is attached to immobilized DNA duplexes at different separations from an electrode and probed electrochemically in the presence or absence of a non-intercalative, redox-active moiety (Abstract). Interruptions in DNA-mediated electron-transfer caused by base-stacking perturbations are reflected in a difference in electrical current, charge and/or potential (Abstract).

In particular, Barton et al. `586 discloses electrodes modified with oligonucleotide duplexes combined with an intercalative, redox-active species (column 6, lines 2 to 5). The different methods for determining the presence of point mutations according to Barton et al. `586 all comprise at least the steps of contacting a first nucleic acid molecule with a second nucleic acid molecule under hybridizing conditions, wherein one of the nucleic acid molecules is derivatized with a functionalized linker, depositing this duplex onto an electrode, contacting the adsorbed duplex with an intercalative, redox-active moiety under conditions suitable to allow complex formation and measuring the amount of electrical current or charge generated (column 6, line 8 to column 7, line 26).

Therefore, all embodiments of the method disclosed by Barton et al. `586 require an intercalative, redox-active moiety. This is confirmed by the specification in column 7, lines 27 to 38 which reads:

> "The invention also relates to the nature of the redox-active moieties. The requirements of a suitable intercalative, redox-active moiety include the position of its redox potential with respect to the window within which the oligonucleotide-surface linkage is stable, as well as the synthetic feasibility of covalent attachment to the oligonucleotide. In addition, chemical and physical characteristics of the redox-active intercalator may promote its intercalation in a site-specific or a non-specific manner. In a preferred embodiment, the redox-active species is in itself an intercalator or a larger entity, such as a nucleic acid-binding protein, that contains an intercalative moiety."

Consequently, it is mandatory for the invention as disclosed by Barton et al. `586 to use a redox-active moiety which intercalates between the base-pairs of a double-stranded DNA

molecule. Thus, Barton et al. `586 not only fails to disclose, teach or even suggest such a specifically claimed feature of the present invention, but in fact teaches explicitly away from the use of a non-intercalative redox active moiety as arguably disclosed in the Lee et al. `653 reference and as recited in claim 58.

Additionally, as noted previously, the enzymes in the Lee et al. `653 reference and as specified in claim 58 of the present application, i.e., alcohol dehydrogenase, lactate dehydrogenase and peroxidase do not exhibit the properties of an intercalator. The Applicant refers to the previously submitted Figs. 1 and 2 from the response of July 15 2003, schematically depicting the structure of alcohol dehydrogenase and lactate dehydrogenase. Both figures clearly show that the respective enzymes do not have a flat or even shape. Please note that fructose dehydrogenase and peroxidase exhibit similar structures.

In view of the above, Barton et al. `586 does not disclose, teach or even suggest in any manner the specifically claimed ".....non-intercalative catalytically redox-active moiety.....", nor that it be, as also specifically claimed, ".....selected from the group consisting of native or modified alcohol dehydrogenase, native or modified fructose dehydrogenase, native or modified lactate dehydrogenase, and native or modified peroxidases".

Furthermore, because Barton et al. `586 teaches specifically away from the use of a non-intercalative catalytically redox-active moiety, no person skilled in the art would replace an intercalator as disclosed by Barton et al. `586 with an enzyme as disclosed in the combined reference of Lee et al. `653, discussed in further detail below, since the presence of an intercalator is mandatory to the invention of Barton et al. `586 as discussed above.

A thorough review of Lee et al. `653 fails to reveal any disclosure, teaching or suggestion to attach these enzymes to an oligonucleotide. Furthermore, besides the fact that Barton et al `586 teaches explicitly away from the use of an intercalative enzyme as explained in detail above, there is nothing in Lee et al. `653 which would lead a person skilled in the art to use the enzymes disclosed therein in the modified nucleic acid oligomer of Barton et al. `586.

Lee et al. '653 discloses immobilization of enzymes and particularly immobilization of glucomylase and other enzymes on glass fibers (column 1, lines 6 to 8). The enzyme is embedded in a matrix coated on the exterior of the glass fibers (column 2, lines 37 to 39). The matrix is comprised of a polymer which has been insolubilized by cross-linking. The degree of cross-linking is controlled to permit penetration by the enzyme substrate which is to react with the enzyme (column 2, lines 39 to 43).

The cross-linking agents used by Lee et al. are bi-functional molecules. Preferred are dialdehydes containing 1 to 10 carbon atoms in addition to the carbon atoms in the aldehyde roups, especially dialdehydes containing 3 to 6 carbon atoms (column 5, lines 29 to 3[illegible]). In addition, polyisocyanates are used, such as toluene diisocyanates, methylene bis-phenyl-4-isocyanate) and poly-phenylene-polymethylene polyisocyanates (column 5, lines 3[illegible] to 3[illegible]).

Lee et al. '653 teaches to control the degree of cross-linking of the polymer by adjusting the amount of cross-linking agent applied (column 2, lines 48 to 50). The activity of the immobilized enzyme can be reduced excessively if too much cross-linking agent is applied. On the other hand, if the amount of cross-linking agent is too low, the enzyme's endurance is reduced (column 2, lines 5[illegible] to 59). The cross-linking agent may also link the enzyme to the polymer, thereby immobilizing it within the matrix (column 3, lines 44 to 47).

There is no teaching, suggestion and/or disclosure as required by case law, which would lead one of skill in the art to combine the enzymes of Lee et al. '653 with a nucleic acid oligomer as specifically recited in claim 58 of the present invention. As the Applicant has made a thorough study of both references, the Examiner is respectfully requested to indicate where in either reference such a suggestion, teaching or disclosure would indicate the potential to support such a combination as asserted by the Examiner. Alternatively, if the Examiner is relying on his/her expertise in this field to support , the Applicant respectfully requests the Examiner to enter an affidavit substantiating the Examiner's position so that suitable contradictory evidence can be entered in this case by the Applicant.

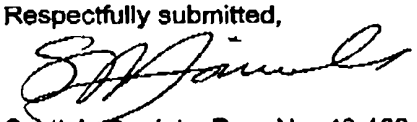
In view of the above amendments and remarks, the Applicant believes claim 58 as amended above to be allowable, and thus the remaining dependent claims 59-86 to be allowable as well. If the Examiner disagrees with the Applicant's view concerning the withdrawal of the outstanding rejections or applicability of the Barton '586 and Lee et al. 653 references, the Applicant respectfully requests the Examiner to indicate the specific passage or passages, or the drawing or drawings, which contain the necessary teaching, suggestion and/or disclosure required by case law.

In view of the foregoing, it is respectfully submitted that the raised rejections should be withdrawn and this application is now placed in a condition for allowance. Action to that end, in the form of an early Notice of Allowance, is courteously solicited by the Applicant at this time.

The Applicant respectfully requests that any outstanding objections or requirements, as to the form of this application, be held in abeyance until allowable subject matter is indicated for this case.

In the event that there are any fee deficiencies or additional fees are payable, please charge the same or credit any overpayment to our Deposit Account (Account No. 04-0213).

Respectfully submitted,



Scott A. Daniels, Reg. No. 42,462
Customer No. 020210
Davis & Bujold, P.L.L.C.
Fourth Floor
500 North Commercial Street
Manchester NH 03101-1151
Telephone 603-624-9220
Facsimile 603-624-9229
E-mail: patent@davisandbujold.com

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Scott A. Daniels